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10/591,608	12/26/2007	Raymond Pratt	61368-233549	3117

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EXAMINER	
CORNET, JEAN P	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,608	PRATT, RAYMOND	
	Examiner	Art Unit	
	JEAN CORNET	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3, 4, 11-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/29/2008 and 09/05/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-10 and the species; donepezil (the compound of formula IV and/or its hydrochloride salt as a cholinesterase inhibitor and atorvastatin as a HMG-CoA reductase inhibitor in the reply filed on 04/30/2009 is acknowledged.

Claims 11-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/30/2009.

. Applicant was supposed to elect a single disclosed cholinesterase inhibitor as per the election of species requirement. However, applicant elects donepezil and/or its salt. Further, applicant did not identify the claims readable on the elected species. Examiner considers the single disclosed elected species as donepezil and its hydrochloride salt, which reads on claims 1, 2, 5-10 for examination on the merit. Claims 3 and 4 of Group I do not read on the elected species and are withdrawn by the examiner.

When responding to this Office Action, Applicant is requested to supply a complete listing of co-pending and/or related applications for each inventor.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claim1,2, 5-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8, 9, 19, 20 and 21 of copending Application No. 12/192,826 and over claims 27, 29 and 30, of copending Application No. 12/073,643 and over claims 1, 2, 6, 7-9 of copending Application No. 09/947,086. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application teaches a

method of treating cerebral autosomal dominant arteriopathy with sucorticol infarcts and leukoencephalopathy (CADASIL). The elected compound of formula IV is donepezil and its hydrochloride salt as a cholinesterase inhibitor and atorvastatin as a HMG-CoA reductase inhibitor.

The copending claims 8, 9, 19, 20 and 21 of Application No. **12/192,826** require treatment of cognitive impairment or dementia caused by a stroke in a patient in need thereof comprising administering a therapeutically effective amount of at least one cholinesterase inhibitor wherein is donepezil, etc...

Copending claims 27, 29 and 30 of Application No. **12/073,643** require treatment of Alzheimer's disease and/or delaying the onset of the disease in a patient in need thereof comprising administering a therapeutically affective amount of donepezil and atorvastatin to the patient.

Copending claims 1, 2, 6, 7-9 of Application No. **09/947,086** require treatment of vascular dementia in a patient in need thereof comprising administering a therapeutically effective amount (5 to 10mg/day, orally) of a compound of formula IV of a pharmaceutically acceptable salt thereof where the compound has donepezil's structure.

The copending claims differ from the instant application in that they all require different disease population with the same compound as the instantly claimed application; donepezil. .

Roman teaches Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is the most common generic form of vascular dementia. This autosomal dominant disorder of small cerebral vessel is caused by mutations in the Notch3 gene (page 430, fourth paragraph). Donepezil hydrochloride as a cholinesterase inhibitor in the treatment of vascular dementia in patient in need thereof has also been used for Alzheimer's patents (page 434, second paragraph).

Kalimo teaches CADASIL is a hereditary cerebrovascular disease leading to cognitive decline and dementia (page371, first paragraph); Kalimo also teaches that Notch3 gene is also found to have some relationship with Alzheimer's disease, AD (page, 371, third paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the invention was made to administer donepezil to treat CABASIL, AD and cognitive impairment or dementia since treatment of one with donepezil would also treat the other ones as suggested by Kalimo and Roman. The drug of the present invention which is the same as the drug set forth in instant Application and the copending Applications can be used as an active ingredient for therapeutic treatment of CADASIL and Alzheimer , since both diseases, if left untreated would lead to cognitive impairment.

Thus, a person of skill in the art would expect donepezil to exhibit the exact same beneficial properties for the treatment of CADASIL as those set forth in the copending Applications when administered to patients in need of such treatment such as those

suffering from AD and dementia or cognitive impairment. See *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) ("From the standpoint of patent law, a compound and all its properties are inseparable.").

In addition, the instant claims 5-7 are directed to oral administration about 1 mg/day to 50 mg/day of donepezil would not be patentably distinct from copending claims 6, 7-9 of Application No. **09/947,086** because the copending claims 6, 7-9 of Application Application No. **09/947,086** teach oral administration of about 5mg/day to 10mg/day of donezepil read on the limitation "oral administration of about 1 to about 5mg/day donezepil orally.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roman et al. (Subcortical ischaemic vascular dementia, "The Lancet Neurology Vol. 1 November 2002") in view of Kalimo et al ("Cadasil: a common form of hereditary arteriopathy causing brain infarcts and dementia" Brain Pathology, 12:371-384, 2002), both cited in the IDS.

.

The claims of the instant application are drawn to a method of treating autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy to a patient in need thereof comprising administering a therapeutically effective amount of donezepil and its hydrochloride salt.

As to claims 1, 2, 5 and 6, Roman teaches that subcortical ischaemic vascular dementia, (SIVD) is major cause of vascular cognitive impairment and dementia due to small arteries disease and hypoperfusion (page 426, second paragraph). Roman also teaches a method of using cholinergic agents such as the well known drug, donepezil hydrochloride as a cholinesterase inhibitor in the treatment of vascular dementia in

patient in need thereof and has also been used for Alzheimer's patients (page 434, second paragraph). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is the most common generic form of vascular dementia. This autosomal dominant disorder of small cerebral vessel is caused by mutations in the Notch3 gene (page 430, fourth paragraph). 5mg/day and 10mg/day donepezil and placebo were administered to patients with Alzheimer's disease and vacular dementia. Patients with vascular dementia showed significant improvement in cognitive scores and global scores (page 434, third paragraph).

As to claims 7 and 8, Although Roman's reference was silent to the form of administration of the drug, it has been demonstrated by Hachiro that donepezil hydrochloride has been inherently administered orally as tablets or parenterally and in the form of injections (page 33 paragraph 97). It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Although Roman does not specifically teach treatment cerebral autosomal dominant arteriopathy with subcortical infarcts leukoencephalopathy, Roman implies that treating vascular dementia with donepezil would also treat CABASIL, because CABSIL is the genetic form vascular dementia.

Kalimo teaches CADASIL is a hereditary cerebrovascular disease leading to cognitive decline and dementia (page371, first paragraph); Kalimo also teaches that Notch3 gene is also found to have some relationship with Alzheimer's disease, AD (page 371, third paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the invention was made to administer donepezil to treat CABASIL, since donepezil has been used to treat AD that has some relationship with the Notch3 gene as suggested by Kalimo. The drug of the present invention which is the same as the drug set forth in Roman can be used as an active ingredient for therapeutic treatment of diseases caused by the Notch 3 gene, for example, CADASIL.

Thus, a person of skill in the art would expect donepezil to exhibit the exact same beneficial properties for the treatment of CADASIL as those set forth in Applicants' invention when administered to patients in need of such treatment such as those suffering from AD. See *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) ("From the standpoint of patent law, a compound and all its properties are inseparable.").

One would have been motivated the combine these references and make the modification because they are drawn to the same technical fields (constituted with same

(or similar) ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Claims 1, 2, 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hachiro et al. (EP1 116 716 A1), in view of Wilkinson et al ("Donepezil in vascular Dementia; a randomized, placebo-controlled study, Neurology", 61:479-486, 2003) and Kalimo et al. ("Cadasil: a common form of hereditary arteriopathy causing brain infarcts and dementia" Brain Pathology, 12:371-384, 2002), both cited in the IDS.

As to claims 1, 2, 7 and 8, Hachiro teaches a method for treating a disease due to acetylcholinesterase activity by administering to a human patient the compound having the formula (XXV) and a pharmacologically acceptable salt thereof (page 4, paragraph 0016), where the preferred compound is 1-benzyl-4-((5,6-dimethoxy-l-indanon)-2-yl)methylpiperidine (page 4, paragraph 15) and its salt (example 4), which is the chemical formula for the well know drug, donepezil. Donepezil has acetylcholinesterase inhibitory action and is effective for treatment of various diseases which are thought to be derived from the deficiency of acetylcholine as neurotransmitter en vivo (page 3, paragraph 0008) and various kinds of dementia and the sequelae of cerebrovascular disease, (page 33, paragraph 0092). Hachiro further teaches that the compound can be

administered orally, in the form of injection. Donepezil has a potent acetylcholinesterase inhibitory action (page 33, table 3).

Applicant's claims differ in that because they require donepezil in the amount of 1 to 50mg/day to treat CADASIL.

As to claims 5 and 6, Wilkinson teaches vascular dementia also known as dementia associated with cerebrovascular disease may benefit from treatment of cholinesterase inhibitors such as donepezil in patients with Alzheimer's (AD) disease plus cerebrovascular disease. Wilkinson further teaches significant benefits cognition, global functions and activities of daily living in patients with mild to moderately severe AD and improvement in patients with vascular dementia (page 479, second paragraph). In a study, donepezil 5 and 10mg/day were administered to patients with probable and possible vascular dementia showed improved coginitive and global function compared with placebo (page 485, third paragraph, right column).

Kalimo teaches that CADASIL is a hereditary cerebrovascular disease, leading to cognitive decline and dementia with a mutation in the Notch3 gene (page 371 first paragraph) with similar risk factors with cerebrovascular disease (page 381, first paragraph, right column). Kalimo further teaches that the Notch3 gene in CABASIL is also found to have some relationship with AD patients (page 371, third paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use acetylcholinesterase inhibitor, donepezil to treat CADASIL when Hachiro is taken in view of Wilkinson and Kalimo, since CABASIL is a hereditay cerebrovascular disease that shares similar risk factors and since vascular dementia is a dementia associated with cerebrovascular disease that benefits from treatment of cholinesterase inhibitor as suggested by Wilkinson, One would have been motivated to administer donepezil to treat CADASIL, because donepezil has acetylcholinerase inhibitory action and is effective for the treament of various kinds of dementia and tcerebrovascular disease, which are thought to be derived from the deficiency of acetylcholine as neurotransmitter en vivo.

Because of the supporting activity of donepezil, the scope of the claims is embraced by the teaching of the cited references.

One would have been motivated to combine the references and use donepezil to treat CADASIL, because Kalimo suggests CADASIL is a hereditary cerebrovascular disease with a mutation in the Notch3 gene shares similar risk factors with cerebrovascular disease and further suggest that the Notch3 gene in CADASIL is also found to have some relationship with AD patients.

One would have been motivated the combine these references and make the modification because they are drawn to the same technical fields (constituted with same (or similar) ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a). Furthermore, administration of donepezil would be beneficial to treat both CADASIL and AD, since the Noth3 gene is also found to be linked to both diseases.

Claims 1, 2, 5-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over John et al (WO 2004/034963) in view of Wilkinson et al ("Donepezil in vascular Dementia. a randomized, placebo-controlled study, Neurology", 61:479-486, 2003) and Kalimo et al. ("Cadasil: a common form of hereditary arteriopathy causing brain infarcts and dementia" Brain Pathology, 12:371-384, 2002), all cited in the IDS.

As to claims 1, 2, 5-10, John teaches a method for treating or delaying the onset of vascular dementia (also known as cerebrovascular dementia) or other dementia in a patient in need thereof by administering a therapeutically effective amount of at least one cholinesterase inhibitor and one statin (page 8, lines 7-10). Donepezil hydrochloride is a preferred cholinesterase inhibitor (page 22, line 1) and atorvastin is an example of the statin (page 8, line 4). The cholinesterase inhibitor, donepezil, can be administered

orally, parentally, by inhalation or by injection (page 23, lines 4-12) ,in a preferred dose of about 5mg/day to 10 mg/day (page 22, line 23),

John does not specifically teach a method to treat CADASIL, but suggests that donepezil can be used with other statins to treat vascular dementia, also known as cerebrovascular dementia.

Wilkinson teaches Wilkinson teaches vascular dementia also known as dementia associated with cerebrovascular disease may benefit from treatment of cholinesterase inhibitors such as donepezil in patients with Alzheimer's (AD) disease plus cerebrovascular disease. Wilkinson further teaches significant benefits cognition, global functions and activities of daily living in patients with mild to moderately severe AD and improvement in patients with vascular dementia (page 479, second paragraph).

Kalimo teaches that CADASIL is a hereditary cerebrovascular disease, leading to cognitive decline and dementia with a mutation in the Notch3 gene (page 371 first paragraph) with similar risk factors with cerebrovascular disease (page 381, first paragraph, right column). Kalimo further teaches that the Notch3 gene in CABASIL is also found to have some relationship with AD patients (page 371, third paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the invention was made to administer donepezil to treat CABASIL, since donepezil has been used to treat AD that has some relationship with the Notch3 gene as suggested by Kalimo. The drug of the present invention which is the same as the drug set forth in Roman can be used as an active ingredient for therapeutic treatment of diseases caused by the Notch 3 gene, for example, CADASIL.

One would have been motivated to combine the references and use donepezil to treat CADASIL, because Wilkinson suggests that cholinesterase inhibitors such as donepezil that has been used for AD treatment would be beneficial for the treatment of cerebrovascular disease and CADASIL, which is a hereditary cerebrovascular disease, leading to cognitive decline and dementia.

Thus, a person of skill in the art would expect donepezil to exhibit the exact same beneficial properties for the treatment of CADASIL as those set forth in Applicants' invention when administered to patients in need of such treatment such as those suffering from AD. See *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) ("From the standpoint of patent law, a compound and all its properties are inseparable.")

One would have been motivated the combine these references and make the modification because they are drawn to the same technical fields (constituted with same (or similar) ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

In conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JEAN CORNET whose telephone number is (571)270-7669. The examiner can normally be reached on Monday-Thursday 7.00am-5.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)? If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JC/

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614